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Letter to editor

Occurrence of Gitelman-like syndrome in a patient on thiazide and proton pump inhibitor☆

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Abbreviations

ADR adverse drug reaction
ECG electrocardiogram
eGFR estimated glomerular filtration rate
ENaC epithelial sodium channel
GS Gitelman syndrome
HCT hydrochlorothiazide
NCC NaCl cotransporter
PPI proton pump inhibitor
PPIs proton pump inhibitors
PTH parathyroid hormone
ROMK renal outer medullary potassium channel
TRPM6 transient receptor potential melastatin 6
WHO-UMC World Health Organization-Uppsala Monitoring Centre

1. Introduction

Gitelman syndrome (GS) is a rare autosomal recessive tubulopathy [1] characterized by metabolic alcalosis, hypokalemia, hypocalciuria, and hypomagnesemia. Patients may present with abdominal pain, vomiting, low blood pressure, facial paraesthesia, muscle weakness, and tetany [2]. Acquired forms are associated with autoimmune diseases [3]. Although uncommon, prolonged use of a thiazide diuretic with a proton pump inhibitor can cause a combination of electrolyte abnormalities and symptoms resembling GS, as the case presented here demonstrates.

2. Case report

A 63-year-old man was referred to the emergency department due to lower limb cramps and paraesthesia. He had a history of hypertension, hypercholesterolemia, and prediabetes, and has been on losartan/hydrochlorothiazide (HCT) and esomeprazole for five years. Physical exam showed diffuse hyperreflexia without muscle weakness or tetany. Despite normal renal function (eGFR 97 mL/min/1.73 m^2; normal > 60), blood tests revealed significant electrolyte disturbances: hypokalemia (2.7 mmol/L; normal range 3.6–4.6), hypomagnesemia (0.44 mmol/L; normal range 0.59–0.83), and hypocalcemia (total calcium 1.74 mmol/L; normal range 2.20–2.52; ionized calcium 0.85 mmol/L; normal range 1.15–1.29). Vitamin D was low at 36 nmol/L (normal > 75), while parathyroid hormone (PTH) was within normal limits at 4.47 pmol/L (normal range 1.10–6.80). Venous blood gas analysis showed metabolic alkalosis, with pH 7.47 (normal range 7.35–7.45) and bicarbonate elevated at 33 mmol/L (normal range 22–26). Spot urine analysis revealed hypocalciuria (< 0.20 mmol/L) and elevated potassium excretion (28.6 mmol/L), whereas the remaining parameters were within the normal range. The ECG was normal. The patient received electrolyte supplementation.

The combination of hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria, despite preserved renal function, is characteristic of GS, a hereditary disorder caused by defective activity of the sodium-chloride cotransporter in the distal convoluted tubule. We suspected an acquired Gitelman-like syndrome due to chronic proton pump inhibitors (PPI) and thiazide use. Both medications were discontinued. Antihypertensive therapy was replaced with valsartan and amlodipine, and the PPI was switched to an alternative antacid. This change led to a gradual improvement in serum electrolyte levels, further supporting our hypothesis. Laboratory findings are detailed in Table 1.

To evaluate the causal relationship between chronic thiazide and PPI administration and the observed adverse event, causality assessment was performed using the French drug reaction causality assessment method. We calculated an intrinsic imputability score of I5 (very likely; C2S3; chronological imputation: C2; semiological imputation: S3) [4,5]. For extrinsic imputability (bibliographic criterion), we assigned a score of B4 for both drugs as the observed electrolyte disturbances are described in the summary of product characteristics. However, reports specifically describing a Gitelman-like syndrome associated with either agent remain limited, with only one case reported in a carrier of a Gitelman syndrome-associated mutation [6]. The case was reported to the national pharmacovigilance center, Swissmedic (worldwide number CH-SM-2025-00927, date first received: 6th February 2025). In the Swiss pharmacovigilance system, we use the WHO-UMC system for causality assessment. In the present case, the causality was assessed as possible for both drugs. Using the Naranjo adverse drug reaction (ADR) probability scale, the total score was 5, suggesting a probable ADR [7]. This ADR was reported according to standard guidelines [8].

3. Discussion

We report a rare case of Gitelman-like syndrome induced by chronic use of esomeprazole and hydrochlorothiazide, leading to severe electrolyte disturbances, including hypokalemia, hypomagnesemia,

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Table 1
Laboratory results before and after thiazide and PPI withdrawal.

Parameter	Initial level	After withdrawal	Reference range	3-month follow-up
Hemoglobin, g/L	142	NA	140–180	NA
Serum creatinine, μmol/L	75	74	62–106	88 (N: 62–115)
eGFR, mL/min/1.73 m^2	97	98	> 60	> 60 (N: > 60)
Serum albumin, g/L	39	39	35–48	50 (N: 34–48)
Serum sodium, mmol/L	144	139	136–144	141 (N: 136–145)
Serum potassium, mmol/L	2.7	4.4	3.6–4.6	5.0 (N: 3.5–5.0)
Serum chloride, mmol/L	99	NA	98–106	NA
Serum calcium, mmol/L	1.74	2.24	2.20–2.52	2.56 (N: 2.18–2.60)
Serum corrected calcium, mmol/L	NA	2.26	NA	2.31 (N: 2.10–2.60)
Serum ionized calcium, mmol/L	0.85	NA	1.15–1.29	1.29 (N: NA)
Serum phosphorus, mmol/L	0.93	1.17	0.80–1.45	NA
Serum magnesium, mmol/L	0.44	0.61	0.59–0.83	0.72 (N: 0.70–1.10)
Serum PTH, pmol/L	4.47	NA	1.10–6.80	NA
1,25-dihydroxyvitamin D, nmol/L	36.0	NA	> 75	NA
pH	7.47	NA	7.35–7.45	NA
Serum bicarbonates, mmol/L	33	NA	22–26	NA
Urine sodium, mmol/L	78	116	NA	167 (N: NA)
Urine potassium, mmol/L	28.6	8.1	NA	56 (N: NA)
Sodium/potassium ratio, %	2.72	14.32	NA	2.98
Urine calcium, mmol/L	< 0.20	1.17	NA	NA
FECa, %	NA	0.912	NA	NA
Urine magnesium, mmol/L	NA	NA	NA	NA
FEMg, %	NA	NA	NA	NA
Urine chloride, mmol/L	37	50	NA	NA
Urine phosphorus, mmol/L	NA	NA	NA	NA
Urine albumin, mg/L	NA	21	0–10	NA
Urine creatinine, mmol/L	NA	4.2	NA	NA
Albumin/creatinine ratio, mg/mmol	NA	5.1	NA	NA
Protein/creatinine ratio, mg/mmol	NA	23.9	NA	NA

eGFR: estimated glomerular filtration rate; FECa: fractional excretion of calcium; FEMg: fractional excretion of magnesium; NA: not available; PTH: parathyroid hormone.

hypocalcemia, hypocalciuria, and metabolic alkalosis. GS is a rare autosomal recessive tubulopathy caused by mutations in the SLC12A3 *gene*, which encodes the thiazide-sensitive NaCl cotransporter (NCC) located in the distal tubule [1]. Acquired forms (pseudo-Gitelman syndrome) are usually associated with autoimmune diseases, such as Sjögren syndrome, systemic lupus erythematosus, and systemic sclerosis [3]. Drug-induced pseudo-Gitelman syndrome have also been described [6].

In our case, hypomagnesemia can result from both proton pump inhibitors (PPIs), through reduced intestinal magnesium absorption [9,10] and the chronic administration of hydrochlorothiazide, which decreases the expression of the epithelial magnesium channel TRPM6 in the distal convoluted tubule. This reduction impairs renal magnesium reabsorption, thereby increasing urinary magnesium excretion and leading to hypomagnesemia [11]. The main other causes of hypomagnesemia were excluded through a comprehensive anamnesis and biological assessment, including chronic excessive alcohol consumption, prolonged gastrointestinal losses such as chronic diarrhea, malnutrition or insufficient magnesium intake, as well as alternative endocrine or renal etiologies.

The patient's hypocalcemia was likely multifactorial, resulting from the complex regulation of phosphor-calcic metabolism. Although low 1,25-dihydroxyvitamin D levels may have contributed to hypocalcemia, hypomagnesemia can also reduce parathormone (PTH) secretion and increase resistance to PTH action [11,12]. Moreover, although a normal PTH level despite severe hypocalcemia suggested primary hypoparathyroidism, normal phosphate levels argue against it, as hypoparathyroidism usually causes hyperphosphatemia.

Moreover, calcium needs to be ionized and in solution to be absorbed. Consequently, profound acid suppression may compromise calcium solubilization and absorption. Esomeprazole therefore appears to be an additional contributing factor to our patient's hypocalcemia, as proton pump inhibitors have been associated with impaired magnesium homeostasis and altered calcium metabolism [13].

Thiazide diuretics can also increase serum calcium levels via enhanced distal tubule reabsorption, which can mask underlying hypocalcemia [14]. In our case, the patient's persistently low calcium levels despite chronic HCT use suggest that the actual degree of hypocalcemia may have been more severe than indicated by the laboratory measurements. We could suggest an underlying magnesium-dependent impairment of PTH secretion and action, exacerbating calcium loss.

The potassium disturbance was also likely due to multiple interrelated factors. Hypokalemia is a well-established consequence of hypomagnesemia, which increases kaliuresis since adequate intracellular magnesium levels are required to suppress the activity of the renal outer medullary potassium (ROMK) channel. Additionally, thiazide diuretics promote potassium wasting by enhancing sodium delivery to the distal nephron, stimulating epithelial sodium channels (ENaC), and increasing potassium excretion via ROMK channels [14]. We also ruled out hyperaldosteronism based on urinary spot testing, which did not reveal an inverted sodium-to-potassium ratio. Therefore, the primary mechanism of hypokalemia was urinary potassium loss secondary to chronic thiazide use and exacerbated by hypomagnesemia.

In conclusion, the synergistic effect of esomeprazole and hydrochlorothiazide likely explains the profound hypomagnesemia observed in our patient, supporting the responsibility of the drug association in the appearance of ionic disorders. Although electrolyte disturbances associated with PPIs and thiazides are well recognized, their synergistic effects remain underexplored.

4. Clinical implications

The constellation of hypokalemia, hypomagnesemia, hypocalciuria and metabolic alkalosis was a key diagnostic indicator of drug-induced Gitelman-like syndrome. Unlike genetic Gitelman syndrome, this acquired form was iatrogenic, induced by the combination of HCT and esomeprazole. Although electrolyte disturbances associated with thiazides and proton pump inhibitors are individually well recognized, the occurrence of a complete Gitelman-like biochemical phenotype induced by their combined use remains uncommon. This presentation therefore represents a potential diagnostic pitfall and highlights the importance of considering medication-induced pseudo-Gitelman syndrome in the differential diagnosis of patients presenting with this biochemical profile.

This case highlights the importance of early recognition of drug-induced pseudo-Gitelman syndrome to prevent severe metabolic complications and avoid unnecessary investigations for inherited tubulopathies. Given the widespread use of these medications, routine monitoring of serum magnesium, potassium, and calcium should be considered in patients receiving long-term therapy with thiazides and PPIs, particularly in those presenting with neuromuscular symptoms.

5. Strengths and limitations

The primary strength of this report is the clear documentation of electrolyte abnormalities and their subsequent correction following drug withdrawal, confirming the iatrogenic nature of the disorder. Additionally, this case contributes to the growing body of literature on acquired Gitelman-like syndromes induced by HCT and PPIs.

However, this study has several limitations that must be acknowledged. First, the absence of data, particularly regarding urinary magnesium excretion following drug withdrawal, represents a constraint that may impact the robustness of our conclusions. Nevertheless, the normalization of serum electrolyte levels after discontinuation of the medication supports the proposed diagnostic hypothesis and argues against an inherited tubulopathy. Second, no historical data on electrolyte levels were available for this patient over the past few years, limiting the ability to assess any pre-existing abnormalities. Third, pre-illness laboratory values were unavailable, limiting our ability to assess electrolyte status before symptom onset.

6. Conclusion

This case underscores the complex interplay between drug-induced electrolyte imbalances and highlights the importance of a thorough medication history and systematic evaluation in patients presenting unexplained electrolyte abnormalities.

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Ethical approval

Not applicable.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying data.

Use of IA in redaction

The authors used a large language model (ChatGPT, OpenAI) to assist with linguistic editing and structuring of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Vargas-Poussou R, Dahan K, Kahila D, Venisse A, Riveira-Munoz E, Debaix H, et al. Spectrum of mutations in Gitelman syndrome. J Am Soc Nephrol 2011;22:693–703.
[2] Knoers NV, Levtchenko EN. Gitelman syndrome. Orphanet J Rare Dis 2008;3:22.
[3] Kim YK, Song HC, Kim YS, Choi EJ. Acquired Gitelman syndrome. Electrolytes Blood Press 2009;7:5.
[4] Miremont-Salamé G, Théophile H, Haramburu F, Bégaud B. Causality assessment in pharmacovigilance: The French method and its successive updates. Therapie 2016;71:179–86.
[5] Moore N, Berdaï D, Blin P, Droz C. Pharmacovigilance – The next chapter. Therapie 2019;74:557–67.
[6] Tursi A. Gitelman syndrome triggered by proton-pump inhibitor use. Dig Liver Dis 2019;51:911.
[7] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
[8] Kelly W, Arellano F, Barnes J, Bergman U, Edwards R, Fernandez A, et al. Guidelines for Submitting Adverse Event Reports for Publication. Therapie 2009;64:289–94.
[9] Gommers LMM, Hoenderop JGJ, De Baaij JHF. Mechanisms of proton pump inhibitor-induced hypomagnesemia. Acta Physiol 2022;235:e13846.
[10] Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin Endocrinol (Oxf) 2008;69:338–41.
[11] Nijenhuis T, Vallon V, Van Der Kemp AWCM, Loffing J, Hoenderop JGJ, Bindels RJM. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest 2005;115:1651–8.
[12] Vetter T, Lohse MJ. Magnesium and the parathyroid. Curr Opin Nephrol Hypertens 2002;11:403–10.
[13] Uehara A, Kita Y, Sumi H, Shibagaki Y. Proton-pump inhibitor-induced severe hypomagnesemia and hypocalcemia are clinically masked by thiazide diuretic. Intern Med 2019;58:2201–5.
[14] Ellison DH, Loffing J. Thiazide effects and adverse effects: insights from molecular genetics. Hypertension 2009;54:196–202.

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